7. (Once Amended) The method of claim 1, wherein said cation exchange resin comprises Sepharose and a carboxy methyl ion exchange group.

REMARKS

The present invention

The present invention resides in the discovery that conventional chromatography techniques can be successfully used to manufacture IgG4 immunoglobulin free of IgG1, IgG2 and IgG3 subtypes for the treatment of diseases and conditions, including serious insect sting allergies. Previously, it had been thought that conventional chromatography techniques were inadequate to separate human IgG subclass proteins into pure fractions. Consequently, more complex methods of protein separation, such as immunoaffinity chromatography, were optimized for IgG subtype purification. These complex methods, however, presented problems of their own.

The present inventors, recognizing the importance of preparing pure and clinically effective IgG4 preparations, found for the first time that conventional ion exchange chromatography can be optimized for the preparation of pure IgG4 suitable for injection into allergic individuals. The IgG4 pure preparations prepared from the methods of the present invention contain less protein and more blocking antibody per unit weight, thereby conferring immunity in patients while reducing the risks of aggregation and fragmentation of the immunoglobulin.

Status of the claims

With this amendment, claims 1 and 5-9 are pending in the present application and under examination. Claims 6 and 7 have been amended. Appendix A provides the version with markings to show change to the claims. Appendix B shows all pending claims currently under examination.

Claims 6 and 7 have been amended to more distinctly claim the present invention. These amendments add no new matter. Support for them can be found, e.g., in the claims as filed and in the general knowledge of those of skill in the art.

For convenience, the Examiner's rejections are addressed in the order in which they were presented in the May 2, 2002 Office Action. Reconsideration is respectfully requested.

Rejections under 35 U.S.C. § 112, first paragraph

Applicant and his representatives wish to thank Examiner Ford for the recent telephonic interview during which the phrase "essentially free" was discussed. During the interview, it was agreed that the phrase "essentially free," as expressed in Claim 1, fully complies with 35 U.S.C. § 112.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 6 and 7 were rejected as allegedly having uncertain scope because the claims contain the terms DEAE Sepharose® and CM-Sepharose®. In response, Applicant has substituted the terms DEAE Sepharose® and CM-Sepharose® with a generic description. This amendment adds no new matter. As stated in the M.P.E.P. §2163.07:

> "a rewording of a passage where the same meaning remains intact is permissible...**The mere inclusion of dictionary or art recognized definitions known at the time of filing an application would not be considered new matter.**" (Emphasis added)

The Applicant asserts that the term "DEAE Sepharose®" is a well known, art-recognized example of an ionic exchanger comprising sepharose and a diethyl aminoethyl ion exchange group. Applicant also asserts that the term "CM-Sepharose®" is a well known, art-recognized example of a cationic exchanger comprising Sepharose and a carboxy methyl ion exchange group. Both exchangers are commercially available from Amersham Biosciences. Under M.P.E.P § 2163.07, the mere inclusion or rewording of art recognized definitions is not new matter.

Accordingly, Applicant respectfully requests that the rejection be withdrawn.

First Rejection under 35 U.S.C. §103(a)

The Examiner has rejected claim 1 under 35 USC § 103(a) as allegedly being obvious over Bird *et al.* (*Journal of Immunological Methods*, 71, 1984, 97-105). The Examiner state on page 5 of the Office Action:

> Bird *et al.* teach a method of separating human serum IgG into subclass fractions which includes IgG4 by immunoaffinity chromatography. Bird *et al.* teach the use of Sepharose columns and DEAE columns. Bird *et al.* teach that the pH for affinity purifications was pH 4-8 for all IgG subclasses.

In response, Applicant respectfully traverses the rejection.

M.P.E.P. § 2143 states the following:

> "[t]o establish a *prima facie* case of obviousness, *three* basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)."

All three elements set forth above must be present in order to establish a *prima facie* case of obviousness. Applicants assert that a *prima facie* case of obviousness has not been established for the following reasons: 1) there is no suggestion or motivation to modify the references; 2) there is no reasonable expectation of success; and 3) the cited art references do not teach or suggest all the claim limitations.

There is no Suggestion or Motivation to Modify the References

Applicant states that there is simply no motivation or suggestion provided in the cited reference to use the methods claimed in the present application to prepare a IgG4 preparation, free of other IgG subtypes. As the Examiner is aware, obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

The reason that there is no motivation or suggestion in the cited reference to prepare IgG4 by conventional ion-exchange chromatography is that Bird *et al.* teaches IgG4 preparation by *immunoaffinity chromatography*, not by conventional ion-exchange chromatography. Bird *et al.* teaches a method of preparing an IgG4 preparation by covalently attaching monoclonal antibodies to an affinity column and subsequently applying human normal immunoglobulin to the column. The use of monoclonal antibodies in combination with affinity columns to purify a protein is known in the art as immunoaffinity chromatography. In brief, immunoaffinity chromatography requires the preparation of monoclonal antibodies and an elution buffer capable of separating the resultant bound antigens from the monoclonal antibodies. Typically, it is difficult to separate the bound antigens, e.g., IgG4, from the monoclonal antibodies. In the Bird *et al.* reference, KCNS, a chemical toxic to humans, is used as the elutant thereby demonstrating that the Bird *et al.* method, although suitable for separating IgG into fractions, is not suitable for the preparation of IgG4 preparations for clinical use.

In contrast, the present application provides methods of using conventional ion-exchange chromatography to separate IgG fractions on the basis of charge characteristics and to thereby manufacture IgG4 preparations suitable for clinical use. Unlike the cited reference, the present application does not teach the attachment of antibodies to the affinity column resin in order to prepare pure IgG4. Accordingly, in the

methods of the present invention, there is no need for monoclonal antibody preparation or for a second purification step to rid the IgG4 preparation of the protein that captured it.

The Examiner points to nothing in the Bird *et al.* reference that teaches the use of conventional chromatography techniques to separate IgG into fractions. Bird *et al.* teaches how to use immunoaffinity chromatography to separate human serum IgG into subclass fractions. The present application teaches that, contrary to expectations, conventional chromatography techniques can be used to prepare purified IgG4.

On page 5 of the Office Action, the Examiner states that Bird *et al.* teaches the use of Sepharose columns and DEAE columns for the purification of IgG into subclass fractions. It must be emphasized that Bird *et al.* teaches the use of the columns with immunoaffinity chromatography techniques, not with conventional chromatography techniques.

In summary, the skilled practitioner would not be motivated to purify IgG4 using conventional chromatography techniques. The law requires that motivation come from a fair reading of all the references. Motivation is not properly set forth when it is supported by taking select language out of context from the cited art and combining that language with the applicant's disclosure. Therefore, Applicant respectfully requests that the Examiner withdraw the rejection.

There is No Reasonable Expectation of Success

In addition to a lack of sufficient motivation to use conventional chromatography techniques to purify IgG4, there is also no reasonable expectation of success that IgG4 can be purified from blood plasma using the methods of the present invention. "Both the suggestion and the expectation of success must be found in the prior art, not the Applicants' disclosure." *In re Dow Chem. Co.*, 5 U.S.P.Q.2d 1529, 1532 (Fed. Cir. 1988).

In fact, not only is there absolutely no teaching or suggestion in the Bird *et al.* reference to modify the teaching therein to arrive at the presently claimed invention, the Bird *et al.* reference actually teaches away from the present invention. As stated in

the MPEP at § 2141.02, "prior art must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention." The first sentence of the Bird *et al.* reference states that conventional chromatography *cannot* be used to separate IgG into its fractions,

> "the physico-chemical characteristics of human IgG subclass proteins are too similar to allow the isolation of pure individual subclass fractions by conventional chromatographic techniques".

Accordingly, at no point in the Bird *et al.* reference is it indicated that anything other than immunoaffinity chromatography can be used to achieve pure IgG subclasses.

The Examiner has pointed to nothing in the cited reference demonstrating that the conventional techniques claimed in the present invention can be used to prepare pure IgG4 preparations suitable for injection into humans. After reading the Bird *et al.* reference, the skilled practitioner would have no expectation of successfully obtaining a IgG4 fraction free of other subtypes suitable for injection into humans by conventional chromatography techniques. Accordingly, Applicant respectfully requests the rejection be withdrawn.

The Cited Art References Do Not Teach All Limitations of the Claims

The prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970). Applicant asserts that the cited references do not teach or suggest all the limitations of the claims and therefore, the obviousness rejection is untenable.

Applicant claims a novel method of manufacturing purified IgG4. The method comprises using conventional chromatography techniques to prepare pure IgG4, e.g., adjusting plasma to a pH of about 6.5 and a conductivity of between 3.5 to 6 millisiemens, contacting the plasma with an anion exchange resin to obtain an anion exchange effluent, and contacting the effluent with a cation exchange resin to obtain a cation exchange effluent that comprises IgG4 essentially free of other IgG subtypes. Under *In re Wilson supra, a prima facie* case of obviousness has not been established as each of the limitations of the claims is not taught or suggested in the cited art reference.

Bird *et al.* does not teach the use of conventional ion exchange chromatography to fractionate IgG4. Furthermore, Bird *et al.* teaches that conventional ion exchange chromatography techniques cannot be used to prepare pure IgG4.

Applicant has demonstrated for the first time that conventional ion exchange chromatography can, in fact, be used to prepare pure IgG4. The cited reference neither teaches nor suggests conventional chromatography techniques for IgG4 purification. Accordingly, Applicants request that the rejection of claim 1 over Bird *et al.* be withdrawn.

SECOND REJECTION UNDER 35 USC § 103(a)

Claims 1 and 5-9 were rejected as allegedly being obvious over Bird *et al.* in view of Laursen *et al.* (U.S. Patent No. 6,281,336). The Examiner alleges on page 7 of the office action:

> It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to use exchange resins DEAE Sepharose® and CM-Sepharose® as taught by Laursen *et al.* in the method of separating human serum IgG into subclass fractions which includes IgG4 by immunoaffinity chromatography as taught by Bird *et al.* because Bird *et al.* teach to obtain a purified IgG4 a second run on appropriate affinity columns may be necessary and Laursen *et al.* teach that the use of DEAE Sepharose® and CM-Sepharose® exchange resins connected in series would provide a high degree of purity and high content of IgG monomers and dimmers which is partly due to the use of two serially connected chromatography columns.

As previously discussed, Bird *et al.* teaches the use of *immunoaffinity chromatography* to separate IgG into fractions. As evidenced in the first sentence of the Bird *et al.* reference, Bird *et al.* teaches away from the use of conventional ion exchange chromatography to separate IgG into fractions.

Laursen *et al.* teaches the use of anion exchange and cation exchange chromatography to purify IgG from a crude immunoglobulin-containing plasma protein

fractions. Nothing in the Laursen *et al.* patent suggests a purification method for separating IgG into its separate fractions. Furthermore, after reading the Bird *et al.* reference, the skilled practitioner would have no reason to believe that anion and cation exchange resins connected in series would be sufficient to prepare purified IgG4.

Not only does the Laursen *et al.* patent neither teach nor suggest the use of exchange resins to prepare IgG4 pure preparations, the purification procedure taught in the Laursen *et al.* patent relies on buffers having a pH and ionic strength sufficient for the elution of pure IgG from the cation exchange resin. In contrast, the exchange resins used in the present methods are optimized for elution of pure IgG4 from the cation exchange resin. One of skill in the art would not expect a purification system for the extraction of pure IgG from crude plasma to be relevant for the purification of an IgG4 subtype from IgG. As explained in the previous response, this is because the art of fractionation and ion exchange chromatography is unpredictable. Therefore, one of skill in the art would not predict that a purification scheme effective for the purification of IgG from crude plasma would be equally effective, or even marginally effective, for the purification of an immunoglobulin subtype IgG4 from an IgG preparation or even the same crude plasma starting material. The Laursen *et al.* patent does not imply otherwise.

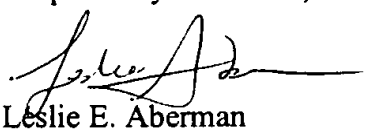
Therefore, because Bird *et al.* does not teach purification of IgG4 by conventional chromatography techniques and Laursen *et al.* does not teach purification methods relevant for IgG4 purification, the instant claims are in no way made obvious. As such, Applicant respectfully requests that the Examiner withdraw the rejection of claims 1 and 5-9 over Bird *et al.* in view of Laursen *et al.*

CONCLUSION

In view of the foregoing, Applicant believes all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-273-4787.

Respectfully submitted,



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See Attached Letter.

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APPENDIX A

VERSION WITH MARKINGS TO SHOW CHANGES MADE

6. (Once Amended) The method of claim 1, wherein said anion exchange resin [is a DEAE Sepharose® resin] comprises Sepharose and a diethyl aminoethyl ion exchange group.

7. (Once Amended) The method of claim 1, wherein said cation exchange resin [is a CM-Sepharose® resin] comprises Sepharose and a carboxy methyl ion exchange group.

APPENDIX B

PENDING CLAIMS SUBJECT TO EXAMINATION

1. (Once Amended) A method of manufacturing IgG4 immune globulin that comprises the steps of:

(a) adjusting plasma to a pH of about 6.5 and a conductivity of between 3.5 to 6 millisiemens;

(b) contacting the plasma obtained from step (a) with an anion exchange resin to obtain an anion exchange effluent; and

(c) contacting the effluent of step (b) with a cation exchange resin to obtain a cation exchange effluent that comprises IgG4 essentially free of other IgG subtypes.

5. The method of claim 1, wherein said plasma is plasma obtained from an immune donor.

6. (Once Amended) The method of claim 1, wherein said anion exchange resin comprises Sepharose and a diethyl aminoethyl ion exchange group.

7. (Once Amended) The method of claim 1, wherein said cation exchange resin comprises Sepharose and a carboxy methyl ion exchange group.

8. The method of claim 1, further comprising the steps of:

(d) adding NaCl to a final concentration of 0.03 to 0.05 M NaCl;

(e) filtering the solution of step (d);

(f) centrifuging the filtrate of step (e);

(g) freezing the supernatant of step (f);

(h) thawing the frozen supernatant of step (g);

(i) adding a monosaccharide or disaccharide to the thawed supernatant of step (h) to a final osmolarity of between 0.22 to 0.35 OsM;

(j) filtering the solution of step (i);

(k) freezing the filtered solution of step (j);

(l) thawing the frozen solution of step (k); and

(m) lyophilizing the solution of step (l).

9. The method of claim 8, wherein said monosaccharide is lactose.